REMARKS

I. Status of the Claims

Claims 33-48 are currently pending, with claims 38-43 withdrawn from consideration as directed to a non-elected invention.

This amendment is deemed to put the case in condition for allowance or in better condition for appeal. Thus, entry of this amendment is respectfully requested in accordance with 37 C.F.R. 1.116.

II. Objections to the Claims

Applicants maintain their assertion that the Office is not following the procedure described in MPEP 803.02 with respect to a species election for the reasons set forth in prior responses. Accordingly, Applicants maintain their right to address this issue later via petition.

III. Claim Rejections under 35 U.S.C. § 112, First Paragraph

A. Enablement

Claims 33-37 and 44-48 stand rejected under 35 U.S.C. § 112, first paragraph, as encompassing subject matter that is not described in such a way that one of ordinary skill could practice the claimed invention without undue experimentation. The Office reiterates three primary reasons for justifying its conclusion, namely, that the specification does not adequately describe: 1) what constitutes an appropriate dosage of the agent; 2) the identity of a sufficient number of agents that are capable of disrupting the binding between ELC and CCX CKR; and 3) diseases that are correlated with CCX CKR activity. These rationales are addressed in turn below.

With regard to the issue of dosage, Applicants first note that the Examiner has the burden of demonstrating that the claims are not enabled. MPEP 2164.04, for example, emphasizes that

> it is incumbent upon the Patent Office, whenever a rejection on this basis [enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to *back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.* MPEP 2164.04 (emphasis added)

In the last response, Applicants directed the Office to sections of the specification that provide guidance on appropriate dosage levels and other sections that list references that provide further guidance (page 41, lines 6-12; and page 44, lines 1-12). The Office simply dismisses this guidance and the cited references as "broad brush assertions." As highlighted in the quotation above, however, such conclusory statements are insufficient to satisfy the Office's burden of demonstrating *why* this guidance is not enabling. Specifically, the Office has not "back[ed] up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." In the absence of such evidence, the rejection on this particular basis should be withdrawn.

The second enablement issue raised in the Office Action is the assertion by the Office that although the specification describes multiple specific agents that modulate CCX CKR binding, these agents do not constitute a representative number of species sufficient to enable the claimed genus. The Office concludes that one of ordinary skill in the art would still have to engage in undue experimentation to identify additional agents with the desired activity, despite the guidance provided in the specification and the specific structures provided.

As the Office knows, the Federal Circuit in its *In re Wands* decision provided useful guidance on determining when experimentation rises to the level of "undue experimentation." The court stated:

> [E]xperimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art . . . *The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In re Wands*, 8 USPQ2d 1400, 858 F.2d 731, 737 (Fed. Cir. 1988) (emphasis added).

Thus, under the test articulated in Wands, experimentation does not rise to the level of "undue" experimentation if *either* of two criterion are met: (1) the experimentation is merely routine, *or* (2) the specification provides a reasonable amount of guidance with respect to the direction experimentation should take. The question with regard to this specific issue is, thus, whether one of ordinary skill in the art could identify a reasonable number of additional active agents *either* by (1) routine experimentation, *or* (2) based upon the guidance provided in the specification. Although only *one* of these criterion needs to be satisfied, Applicants submit that *both* are satisfied here.

With respect to the first criterion, the Baggiolini reference (J. Internal Med. 250:91-104, 2001) cited in the Office Action, for example, states that "[t]esting for chemokine antagonists is *simple*" (Baggiolini, page 101, last sentence of column 1; emphasis added). Moreover, as pointed out in the last response, the specification provides considerable guidance on specific methods that can be used to screen compounds (see, e.g., page 33, line 29, to page 38, line 7; and example 7). Baggiolini further indicates that certain model systems for studying various diseases associated with chemokines were known as of the priority date of the instant application (Baggiolini, pages 97-99, in section entitled "Chemokines in disease."). The specification lists several more (see, e.g., page 36, lines 16-27). Applicants, thus, submit that in

addition to the specific agents provided in the specification, a reasonable number of additional active agents could have been identified by one of ordinary skill using *routine* methods. So, although the process of screening agents to identify ones with the desired activity may have required considerable experimentation, such experimentation would not be "undue" because the methods for screening the agents was "routine" as of the priority date of the application. This is all that the law requires.

Furthermore, the chances of successfully identifying active agents in such screening methods are significantly enhanced because, as described below, the guidance provided in the specification informs the choice of the type of agents that would have an improved likelihood of being active. So for these reasons alone, Applicants submit that undue experimentation would not be required to identify additional active agents beyond those already described.

Identification of additional active agents is also enabled on a second basis, because the specification provides considerable guidance in the direction that experimentation should proceed. This satisfies the second *In re Wand* criterion set forth above. For example, as pointed out in the last response, the specification provides three exemplary molecules that modulate the activity of CCX CKR. One of skill would recognize that one logical starting point for identifying a number of additional active agents would be to use these molecules as a scaffold or basis from which modifications could be made.

Before proceeding further, Applicants address the statement in the Office Action that these three small molecules provide "little guidance" because "[a]ccording to the specification, these compounds modulate CCX CKR activity rather than CCX CKR binding to ELC" (Office Action, page 6). This is incorrect. Example 7 describes an experiment in which competitive assays were conducted with radiolabeled ELC to identify agents that modulated the ability of ELC to binding CCX CKR. The specification at page 59, lines 6-7, explicitly states that the three small molecules listed on page 38 were found either to inhibit or enhance the binding of ELC to CCX CKR.

Thus, the disclosure in the specification of three high affinity CCX CKR chemokine ligands (ELC, SLC, TECK), as well as another three chemokine ligands that bind with lower affinity (mMIP-1γ), BLC and vMIPII), provides considerable additional structural guidance on the identification of additional modulators of CCX CKR (see, e.g., Example 5). Thus, one of ordinary skill would recognize that another option would be to modify these chemokine ligands to obtain inhibitors, for example. These modified polypeptides could be, for example, truncated forms of these chemokines, chemically modified forms, and peptidomimemtics based upon these ligands (see, e.g., page 11, lines 5-24; and page 20, lines 1-14).

This conclusion is fully consistent with the cited Baggiolini reference. Baggiolini describes, for example, the successful production of a variety of polypeptide antagonists based upon the structure of a number of different chemokine ligands that were effective antagonists of their cognate receptors (see, e.g., Baggiolini, page 101, column 1, first paragraph). Most of the reports Baggiolini summarizes were conducted before the priority date of the instant application. Baggiolini further notes that such chemokine analogues "proved effective in animal models of inflammatory pathologies" (Baggiolini, page 101, column 2, second paragraph). Baggiolini, thus, supports Applicants' view that the skilled practitioner armed with the extensive knowledge provided in the specification concerning CCX CKR ligands could have readily obtained agents that modulate the activity of CCX CKR without undue experimentation. In this regard, it is also important to note that the specification also identifies over 30 chemokines or chemokine related molecules that are not ligands for CCX CKR. The skilled practitioner would recognize that agents having structural similarity to these molecules would likely be poor modulators of CCX CKR activity. The specification, thus, also provides considerable guidance to the skilled practitioner on the direction that research should *not* proceed which, of course, is very beneficial in honing in on additional agents that have the desired activity.

The application also provides guidance in the development of inhibitory antibodies. Methods for preparing such antibodies are described, for example, at page 29, line 21, to page 33, line 4.

The application, thus, provides considerable guidance on the direction that the skilled practitioner could take (or guidance on directions not to take) to identify additional small molecules, as well as peptides and antibodies that had the desired ability to modulate CCX CKR. So for this reason also, a representative number of modulators of CCX CKR are enabled.

The Office's third specific enablement concern is that the specification does not establish a correlation between a disease and CCX CKR activity. In response, Applicants reiterate the points made in the last response, namely that the specification provides an extensive discussion of diseases that can be mediated by CCX CKR activity. Because CCX CKR is a chemokine receptor, this receptor would be expected to be involved in those diseases correlated with chemokine activity. As noted in the background section of the specification, chemokines play a key role in inflammatory responses, leukocyte trafficking , angiogenesis and other processes that involve migration or activation of cells (see, e.g., page 1, lines 18-23). The specification also identifies a number of specific diseases associated with such activities that can be treated with CCX CKR modulators (see, e.g., page 39, line 19, to page 40, line 17). The cited Baggiolini reference supports this view, stating that a "vast literature documents the expression of multiple chemokines in inflamed tissues" and that chemokine receptors and chemokine ligands are routinely involved in various inflammatory conditions (see, e.g., Baggiolini, page 97, column 2, section on "Chemokines in disease").

A role for CCX CKR in various inflammatory conditions is, thus, fully consistent with the activity of other chemokines. It is again noted that the burden is on the Office to prove the contrary, and to back up its assertions with acceptable evidence or reasoning.

B. Written Description

Claims 33-37 and 44-48 are rejected under 35 U.S.C. § 112, first paragraph, because the claims are said to encompass subject matter that is not described in the specification in such a way as to reasonably convey that the inventors were in possession of all that is claimed. For the reasons that follow, Applicants respectfully disagree.

Under the Written Description Guidelines ("Guidelines") (Fed. Reg., vol. 66, page 1106, January 5, 2001), the written description requirement can be satisfied in various ways, including: (1) actual reduction to practice, (2) reduction to drawings, or (3) disclosure of relevant identifying characteristics. Here, Applicants have provided the detailed chemical structure for three different small molecule modulators of CCX CKR, thus satisfying criterion (1). These agents include both antagonists and an agonist. As described above, the skilled practitioner could readily identify additional small molecules based upon these structures.

Applicants have further provided the chemical structures of at least six different chemokines (polypeptides) that bind with high or moderate affinity to CCX CKR. As pointed out in the previous section, the cited Baggiolini reference supports the view that modulators of CCX CKR could be readily prepared once the skilled practitioner knew the ligands for the receptor, knowledge which the instant specification provides for the first time. As also pointed out above, the specification provides considerable detail on molecules that do not inhibit binding between CCX CKR and a cognate ligand, thus providing guidance on classes of molecules likely not to have the desired activity. Thus, at least a second class of compounds (e.g., peptide variants and/or mimetics) are adequately described under criterion (3).

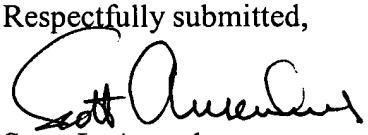
Antibodies that modulate CCX CKR are also readily identified based upon the disclosure in the specification as described above. So a third class of agents is also adequately described.

Applicants have, thus, provided sufficient description with respect to three distinct classes of agents within the claimed genus, specifically small molecules, peptide analogues and antibodies. This fully satisfies the written description requirements for a genus. To the repeated assertion in the Office Action that the small molecules described in the application modulate CCX CKR activity rather than the ability of ELC to bind CCX CKR, Applicants reiterate the point made above, namely, that this simply is not the case. The Office also contends that the claims encompass antisense and triplex oligonucleotides, and that these are not adequately described. Agents within these classes, however, are, in fact, not encompassed by the claims. The claims require the ability to inhibit or modulate binding between a chemokine that is recited in the claims and CCX CKR. These molecules do not exert their inhibitory action in this manner. Rather, antisense and triplex oligonucleotides act by inhibiting expression of CCX CKR. Thus, this concern is not applicable to the presently pending claims.

For all these reasons, Applicants submit that the specification adequately describes the subject matter encompassed by the current claims. Accordingly, it is requested that this rejection be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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